ETHIOPIAN FOOD AND DRUG AUTHORITY

Medicine Evaluation and Marketing Authorization Lead Executive office

Guideline for Registration of Vaccine

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001	New Document Developed	02/2018
002	Amended in line with WHO-GBT audit recommendation to revise the naming of the MA function in line with the new Nomenclature	20/12/2023

Seble Shambel

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ACKNOWLEDGEMENTS

The Ethiopian Food and Drug Authority (FDA) would like to acknowledge and express its appreciation of the United States Agency for International Development (USAID) and the U. S. Pharmacopeial Convention Promoting the Quality of Medicines Program (USP/PQM) for the financial and technical support and United Nations Population Fund (UNFPA) for financial support delivered in the adaption of this Guideline forRegistration of Vaccines.

The Authority would also like to acknowledge its staff and all experts who provide their help hands for the invaluable contributions in the development of this document.

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FORWARD

Ethiopia has been made huge strides to improve access to safe, quality and efficacious medicines including vaccines to the public. The Ethiopian Food and Drug Authority is responsible to ensure the safety, quality and effectiveness of vaccines. Vaccines are pharmaceutical products that fall in this jurisdiction and must be regulated as stipulated in the proclamation No. 1112/2019.

Vaccines are products of biological origin which exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents and adults. The practice of registering vaccines as conventional medicine registration procedure is not acceptable as the regulatory requirements need to be proportional to the nature and the level of risk of the vaccines. This urges to establish special regulatory requirements for registration of vaccine that addresses its unique nature.

The authority is striving to establish robust system that strengthen the evaluation process for quality, safety and efficacy of vaccines for human use and ensuring compliance for Good Manufacturing Practices (GMP). In this guideline, the authority has set the required procedures and requirements for vaccine dossier assessment. I believe that successful implementation of this guideline will help us to achieve access to safe, quality and effective vaccines to the community. Hence, I call up on health professionals, pharmaceutical organizations, development partners and all stakeholders to put a coordinated effort to realize this guideline.

I have no doubt that with the commitment and engagement of the applicants for market authorization to comply with the regulatory requirements and the support of our development partners, we will prevail to implement the aforementioned guideline.

Finally, I would like to take this opportunity to acknowledge and express my appreciation to the United States Agency for International Development (USAID) and the U. S. Pharmacopeial Convention Promoting the Quality of Medicines Program (USP/PQM) for financial and technical support, United Nations Population Fund (UNFPA) for financial support and to all those experts who have directly or indirectly extended their helping hands in preparation of this guideline.

SEBLE SHAMBEL
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1. INTRODUCTION

The Ethiopian Food and drug Authority is mandated by the proclamation Nº. 1112/2019 to ensure the safety, quality and efficacy of medicines. Vaccines are pharmaceutical products that fall in this jurisdiction that must be available in the market of Ethiopia of required safety, quality and effectiveness. Vaccines are products of biological origin that exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents and adults. The quality of a vaccine cannot be assessed solely by testing the final product alone. Hence, specific regulatory systems for vaccines should also be strengthened.

A basic function of the Authority is to evaluate the quality, safety and efficacy of vaccines for human use. In order to license a vaccine for human use, the Authority must first set requirements for applicants to comply with. These requirements include (i) information needed for the application; (ii) evidence that the vaccine has passed the stages of research, development, production and quality control; (iii) evidence from clinical testing, and (iv) evidence that quality, safety and efficacy of the vaccine has been established.Another important aspect to consider in the vaccine evaluation process is that the manufacturing facilities must comply with Good Manufacturing Practices (GMP).

The document is adapted from Guidance Document Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application, Health Canada, 2016 and is based on the requirements of the International Conference on Harmonization (ICH) Common Technical Document (CTD) and the Technical Report Series of the World Health Organization.

This document consists of five modules, following the guidelines established by the ICH CTD, adapted specifically to the registration of vaccines. For those vaccines approved by stringent regulatory authorities, this guideline also pointed out the specific requirements during dossier review process as indicated in Annex IV.

All users of this guideline are strongly invited to forward their comments and suggestions to the Ethiopia Food and Drug Authority of Ethiopia, P.O.Box 5681, Tel. 251-11 552 41 22, email: contactefda@efda.gov.et Addis Ababa, Ethiopia.

2. OBJECTIVES

The objective of this document is to establish requirements for the submission of registration applications for vaccines for human use.

3. SCOPE

This document applies to all vaccines to be authorized for human use, regardless of where they are manufactured, whether they are licensed in the country of origin or not. This document is specific to the filing of New Drug Submissions.

Guideline on variation applications to registered vaccines 1st edition august 2022

For guidance specific to re-registration applications, applicant may refer the Guidelines for Registration of Medicine, 2014, Appendix 4.

4. MODULE 1: ADMINSTRATIVE AND PRODUCT INFORMATION

4.1. COVERING LETTER

Dated and signed letter for submission of the dossier by mentioning the product included in the dossier from the manufacturer responsible for registration. The letter should declare that the information provided in the dossier is true and correct.

4.2. TABLE CONTENTS OF THE DOSSIER

Table of contents should be provided.

4.3. APPLICATION FORM

Completed and signed application form as provided in Annex I of this Guideline should be submitted. The date of application should correspond to the date of submission of the registration dossier to the Authority.

4.4. AGENCY AGREEMENT

i. An agency agreement should be made between the manufacturer of the product for registration and the agent responsible for the import, distribution, and sale of the product in Ethiopia. Where the company manufactures the product at two or more places, the agreement and responsibility of each party made between the manufacturers should be submitted. In such a case, the agency agreement between the local agent and the

manufacturer

Should be the site where the file is kept and the applicant for registration is registered.

ii. The agreement should be signed by both parties and such is what is to be presented. The seal/stamp of both parties should also be affixed to the document for agency agreement.

iii. The agreement should specify the first agent to handle the vaccine registration process. In case the manufacturer has more than one distributor, this has to be mentioned in the agreement. The appointed agent(s) is responsible for correspondence and complete compliance with regulatory requirements pertaining to the product distribution life cycle in the country.

iv. The agreement should state that if any fraud or unsuspected and unacceptable adverse event occurs to the consumer under normal utilization, all the party‟s (local agents, manufacturer, and/or license holder)mentioned in the agreement will be responsible for collecting the product from the market and will be responsible for substantiating any related consequences.

v. The agreement should specify that both parties are responsible for pharmacovigilance and post-marketing reporting of the product safety, quality, and efficacy follow-up after marketing.

vi. For the purpose of administration, the agreement should remain valid for the period of one year from the date of submission to the Authority unless it is found to be satisfactory for the termination of the agreement.

vii. The agent representing the manufacturer for importation should hold a license issued by the Ministry of Trade and a certificate of competence issued by the Authority at the time of importation of the product.

viii. In case the actual manufacturer has scientific office in Ethiopia, the agency agreement should indicate that the scientific office may be responsible for registration of medicines and the local agents are responsible for import and distribution.

4.5. GOOD MANUFACTURING PRACTICE AND CERTIFICATE OF PHARMACEUTICAL PRODUCT

A valid Good Manufacturing Practice (GMP) Certificate and market authorization certificate should be provided. Certificate of pharmaceutical product as a requirement for registration could be optional provided that valid cGMP Certificate or Market Authorization Certificate is submitted. The format of the CPP is provided in Annex II of this Guideline. The CPP should be valid. The CPP for the products should be in line with the explanatory notes of the CPP as provided in Annex III of this Guideline.

4.6. REGULATORY SITUATION IN OTHER COUNTRIES

The countries should be listed in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred, or withdrawn.

4.7. PRODUCT INFORMATION

Product information including package insert, labeling, and summary of product characteristics (SmPC) should be provided. All product information label statements are required to be in English. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification.

4.7.1. Summary of product characteristics

Recommended format for the content of the SmPC is provided in Annex III of this Guideline.

4.7.2. Labeling (immediate and outer label)

Only original labels or computer-ready color-printed labels are accepted for final approval. In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, photocopies of these labels will be accepted for approval.

The titles for batch number, manufacturing, and expiry dates should be part of the printing (typewritten materials, stickers, etc., are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a written

commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

a. The name of the product– brand and generic/International Non-proprietary Name (INN);
b. Pharmaceutical form and route of administration;
c. Qualitative and quantitative composition of active ingredient(s),preservative(s), and antioxidant (s);
d. The volume of the contents, and/or the number of doses, or quantity in container;
e. Directions to consult the package insert or the carton label for complete directions for use;
f. Handling and storage conditions;
g. License number of the manufacturer;
h. Batch number;
i. Manufacturing date;
j. Expiry date; and,
k. Name and address of manufacturer.

4.7.3. Patient Information Leaflet (PIL) or Package Insert

The general content of the PIL should be prepared in line with the content of the SmPC. The PIL should not be described or presented in a manner that is false, misleading, or deceptive or is likely to create an erroneous impression regarding its use in any respect, either pictorially or in words.

4.8. EVIDENCE FOR AN APPLICATION FEE

Each application should be accompanied by a relevant service fee for registration. Applicants are advised to contact the Authority for the amount and details of mode of payment.

5. MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological); nonclinical and clinical information presented in modules 3, 4, and 5 in the registration application. When preparing these summaries, applicant should take an objective approach to the decisive

points related to the quality of the vaccine; clinical and nonclinical studies performed; report all pertinent data for the assessment; and, refer to the corresponding tables included in modules 3, 4, and 5.

Additional information for the preparation of this section can be found in the latest versions of the ICH M4Q, M4S and M4E guidelines. The information in module 2 should be presented in the following order:

2.1 Common Technical Document Table of Contents (Modules 2-5)

A general index should be included of the scientific information contained in modules 2 to 5. The table of contents should be provided.

2.2 CTD Introduction

A summary of the type of vaccine, composition, immunological mechanism, and indications proposed for the vaccine.

2.3 Quality Overall Summary

A general summary of the quality of the vaccine should be presented, related to the chemical, pharmaceutical, and biological aspects. This summary should refer exclusively to the information, data, and justifications included in module 3 or in other modules of the dossier. For example, if the dossier describes more than one drug substance, manufacturer, dosage form, formulation, type of packaging, and/or strength, the applicant should summarize this information in the Quality Overall Summary (QOS) using a similar format as in the Module 3.2 Body of Data. The format should be as follows:

Introduction

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It is important to note that the Drug Substance refers to the vaccine component or antigen, and the Drug Product refers to the final product.

2.3.S Drug Substance (Name, Manufacturer)

2.3.S.1 General Information (name, manufacturer)

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.3 Characterization (name, manufacturer)

2.3.S.4 Control of Drug Substance (name, manufacturer)

2.3.S.5 Reference Standards or Materials (name, manufacturer)

2.3.S.6 Container Closure System (name, manufacturer)

2.3.S.7 Stability (name, manufacturer)

2.3.P Drug Product (Name, Dosage Form)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

2.3.P.2 Pharmaceutical Development (name, dosage form)

2.3.P.3 Manufacture (name, dosage form)

2.3.P.4 Control of Excipients (name, dosage form)

2.3.P.5 Control of Drug Product (name, dosage form)

2.3.P.6 Reference Standards or Materials (name, dosage form)

2.3.P.7 Container Closure System (name, dosage form)

2.3.P.8 Stability (name, dosage form)

2.3.A Appendices

2.3.A.1 Facilities and Equipment (name, manufacturer)

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

2.3.A.3 Excipients

2.3.R Regional Information

2.4 Non clinical Overview

An integrated and critical assessment of the nonclinical evaluation of the vaccine should be provided. The Nonclinical Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology

- Pharmacokinetics

- Toxicology
- Integrated overview and conclusions
- List of literature references

2.5 Clinical Overview

A concise discussion and interpretation of the clinical data should be presented. The Clinical Overview should present the strengths and limitations of the clinical development program and study results, and analyse the benefits and risks of the vaccine in its intended conditions for use.

The format for the Clinical Overview should be as follows:

2.5.1 Product Development Rationale

A discussion of the rationale for the development of the vaccine should be presented.

2.5.2 Overview of Biopharmaceutics

Biopharmaceutical studies are not generally performed for vaccine development. Summary of bioanalytical methods used to assess the immunogenicity of the vaccine in clinical trials should be provided in section 2.5.4.

2.5.3 Overview of Clinical Pharmacology

Pharmacokinetic studies are generally not required for vaccines. However, such studies may be applicable in certain situations, such as the evaluation of vaccine formulations containing new adjuvants.

For vaccines, pharmacodynamics studies generally consist of the immunogenicity studies used to characterize the immune response to the vaccine. A summary of the immunogenicity results should be included in section 2.5.4.

2.5.4 Overview of Efficacy

A critical analysis of the clinical data pertinent to the efficacy of the vaccine in the intended population should be presented. The analyses should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information.

2.5.5 Overview of Safety

A concise critical analysis of the safety data should be presented noting how results support and

justify the proposed prescribing information.

2.5.6 Benefits and Risks Conclusions

This section should provide a concise overall appraisal of the benefit risk assessment by integrating all of the conclusions reached in the previous sections about the safety and efficacy of the vaccine.

2.5.7 Literature References

2.6 Non clinical Written and Tabulated Summaries

The format for the Nonclinical Written and Tabulated Summaries should be as follows:

2.6.1 Introduction

An introduction to the vaccine and its proposed clinical use should be presented.

2.6.2 Pharmacology Written Summary

The format should be as follows:

2.6.2.1 Brief Summary

2.6.2.2 Primary Pharmacodynamics

2.6.2.3 Secondary Pharmacodynamics

2.6.2.4 Safety Pharmacology

2.6.2.5 Pharmacodynamic Drug Interactions

2.6.2.6 Discussion and Conclusions

2.6.2.7 Tables and Figures

2.6.3 Pharmacology Tabulated Summary

If applicable, summary tables for the pharmacology studies should be presented.

2.6.4 Pharmacokinetics Written Summary

This type of studies is generally not performed for vaccines. However, biodistribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors.The feasibility of such studies should be evaluated on a case-by-case basis. If applicable, the formatfor the written summary of pharmacokinetic studies should

be as follows:

2.6.4.1 Brief Summary

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic Drug Interactions (nonclinical)

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and Figures

2.6.5 Pharmacokinetics Tabulated Summary

Pharmacokinetic studies are not generally performed for vaccines. However, for live attenuated vaccines (viral or bacterial including vaccine vectors) there are potential causes of clinically significant infections in the recipient or in contacts.

Summaries of studies providing information on shedding, reversion characteristics and transmission to contacts should be provided here. If applicable, summary tables for the pharmacokinetics studies should be presented.

2.6.6 Toxicology Written Summary

A written summary of toxicology studies should be presented. Refer to guidelines provided for Module 4 below. The format for the Toxicology Written Summary should be as follows:

2.6.6.1 Brief Summary

2.6.6.2 Single-Dose Toxicity

2.6.6.3 Repeat-Dose Toxicity

2.6.6.4 Genotoxicity

2.6.6.5 Carcinogenicity

2.6.6.6 Reproductive and Developmental Toxicity

2.6.6.7 Local Tolerance

2.6.6.8 Other Toxicity Studies

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

2.6.7 Toxicology Tabulated Summary

Summary tables for the toxicology studies should be presented.

2.7 Clinical Summary

A detailed, factual summary of all clinical data should be presented. This includes information provided in clinical study reports, information obtained from any meta analyses or other cross-study analyses, for which full reports have been included in Module 5; and post-marketing data for vaccines that have been marketed in other regions.

The format for the Clinical Summary should be as follows:

2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods

Biopharmaceutical studies are not generally performed for vaccine development. A summary of the bioanalytical assays used to assess vaccine immunogenicity in clinical trials should be provided in section 2.7.3.

2.7.2 Summary of Clinical Pharmacology Studies

Pharmacokinetic studies are generally not required for vaccines. However, such studies may be applicable in certain situations, such as the evaluation of vaccine formulations containing new adjuvants. If applicable, the format of the summary should be as follows:

2.7.2.1 Background and Overview

2.7.2.2 Summary of Results of Individual Studies

2.7.2.3 Comparison and Analyses of Results across Studies

2.7.2.4 Special Studies

2.7.2.5 Appendix

2.7.3 Summary of Clinical Efficacy

For vaccines this section should also include a summary of immune response data that supports

the selection of dose, dosage schedule, and formulation of the final product.

The format of the Summary of Clinical Efficacy should be as follows:

2.7.3.1 Background and Overview of Clinical Efficacy

This section should present a description of the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought.

For vaccines, immunogenicity studies are usually conducted to characterize the immune response to the vaccine and to support vaccine efficacy. An overview of the scientific rationale, the criteria used for the selection of analytical methods for immunogenicity, and the cut-off /threshold values applied should be provided. In addition, information on the performance characteristics of assays including the validation (e.g. linearity range, sensitivity, specificity) and quality control (e.g. accuracy and precision) should be included. This section should not include detailed information about individual studies.

2.7.3.2 Summary of Results of Individual Studies

A tabular listing of all studies providing (or designed to provide) information relevant to vaccine efficacy should generally be provided, together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g. similar to an abstract for a journal article, and should describe critical design features and critical results.

2.7.3.3 Comparison and Analyses of Results across Studies

Using text, figures, and tables as appropriate, a summary of all available data that characterize the efficacy of the vaccine should be presented. This summary should include analyses of all data, irrespective of their support for the overall conclusions and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other.

Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The format of this section is:

2.7.3.3.1 Study Populations

2.7.3.2.2 Comparison of Efficacy Results of all Studies

2.7.3.3.3 Comparison of Results in Sub-populations

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

2.7.3.6 Appendix

2.7.4 Summary of Clinical Safety

A summary of data relevant to safety in the intended vaccine recipient population, integrating the results of individual clinical study reports as well as other relevant reports should be presented. The safety profile of the vaccine, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with the use of tables and figures.

The format of the Summary of Clinical Safety should be as follows:

2.7.4.1 Exposure to the Drug

2.7.4.1.3 Demographic and Other Characteristics of Study Population

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

2.7.4.2.2 Narratives

2.7.4.3 Clinical Laboratory Evaluations

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

2.7.4.5 Safety in Special Groups and Situations

2.7.4.6 Post-marketing Data

2.7.4.7 Appendix

2.7.5 Literature References

A list of references cited in the Clinical Summary should be provided.

2.7.6 Synopses of Individual Studies

This section should include the table entitled Listing of Clinical Studies, described in guidance for Module 5, followed by all individual study synopses organized in the same sequence as the study

reports in Module 5.

6. MODULE 3: QUALITY

The Quality information submitted under Module 3 should be up-to-date, comprehensive, appropriately detailed, relevant, and to the extent sufficient to support the approval of a vaccine submission. A properly completed Module 3 will facilitate preparation of the Quality Overall Summary (QOS) and will expedite the dossier review process.

The Drug Substance refers to the vaccine component or antigen. For a vaccine containing more than one drug substance, the entire Module 3.2.S Drug Substance for one drug substance should be followed by the entire Module 3.2.S Drug Substance for the next drug substance and then followed by the entire 3.2.P Drug Product. The name of the Drug Substance should be included in the heading of all applicable sections and subsections to clearly distinguish the information for each Drug Substance.

For a vaccine with more than one dosage form or for a vaccine supplied in multiple components, e.g. lyophilized powder with a reconstitution diluent, the entire Module 3.2.P Drug Product for one component or dosage form should be followed by the entire Module 3.2.P Drug Product for the next component or dosage form. The name of the component or dosage form should be included in the headings of the corresponding Module 3 sections.

Additional information for the preparation of this section can be found in ICH M4Q (R1), as well as WHO recommendations for the production and control of specific vaccines and other relevant international regulatory guidelines.

3.1 Table of Contents of Module 3

The table of contents should be provided.

3.2 Body of Data

3.2.S Drug Substance (Name, Manufacturer)

The information requested under this point should be supplied individually for each antigen in the vaccine.

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Trade and/or non-proprietary name of the drug substance, based on the WHO or Pharmacopoeia requirements, as appropriate should be provided.

3.2.S.1.2 Structure (name, manufacturer)

Structural formula, molecular formula, and relative molecular mass (if applicable) of the antigen/drug substance should be provided. The schematic primary sequence such as amino acid sequence indicating glycosylation sites or repeating units of polysaccharide indicating modification sites or other posttranslational modifications and relative molecular mass should be provided, if applicable.

3.2.S.1.3 General Properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance, including immunological characteristics and other biological activity, if applicable.

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibilities of the manufacturer(s) involved in the manufacture of the antigen/drug substance should be listed including specific unit or block.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

A description of the manufacturing process should be provided. The description of the manufacturing process should include all of the stages of manufacture. A typical production process for a vaccine starts with a vial(s) from the respective seed and/or cell bank, including cell cultures, harvest(s), purification, modification reactions (when applicable), filling, storage, and transfer/shipping conditions. Where applicable, include the number of passes.

- Flow chart of manufacturing process showing all of the manufacturing steps, including intermediate processes.
- Batch(es) and Scale Definition: An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided. Since pooling may occur at more than one step, it may be more appropriate to describe the batch size and scale under the respective step(s), both within the flow diagram(s) and in the detailed description.

- Cell culture and harvest: A description of the cell culture, seed culture and harvest from the original inoculum up to the last harvesting operation.
- Description of inactivation or detoxification process. Methods and agents used, parameters controlled, and production stage in which it is performed, when applicable.
- Description of purification process. Method, reagents, and materials used, operating parameters controlled, and specifications. Conditions for the use and reuse of membranes and chromatography columns and the respective validation studies should be provided.
- Description of the conjugation process. Indicate when applicable and/or when a modification of drug substance is performed. Also include information on the origin and quality control of the starting material used to obtain the substance used as a protein carrier.
- Stabilization of the drug substance. Description of the steps performed to stabilize the drug substance, for example, the addition of stabilizers or other procedures, when applicable.
- Reprocessing. Description of the procedures established for reprocessing the drug substance or any intermediate product; criteria and justification.
- Filling procedure for the active ingredient, in-process controls. Description of the procedure for packaging the drug substance, process controls, acceptance criteria, type of container closure system, type of seal on the container used to store the drug substance, storage and transfer conditions, when applicable.
- Storage and shipping conditions. When applicable, describe the equipment used, areas and buildings (if pertinent) and the shipping and storage conditions for the drug substance.

3.2.S.2.3 Control of Materials (name, manufacturer)

General description of the starting materials should be provided. All materials used in the manufacturing of the drug substance are expected to be indicated in this section, along with their control measures. For biologically sourced starting materials, information regarding the source, manufacture and characterization should be provided. For vaccines the following information is also expected to be provided in this section as appropriate:

- Summaries of viral safety information (details to be provided in 3.2.A.2).

- Strain: Information on the origin, number of passes, identification, analysis certificates, processes of attenuation, development or construction and genetic stability, depending on the type of vaccine strain.
- Master/Working/Seed Banks Systems. Origin, identification, characterization, preparation method, analysis certificates, adventitious agents testing, stability, controls, and frequency of the tests, definition of the number of passes should be included. In the case of cell banks, demonstrate that the characteristics of the cells remain unaltered in the passes used in production and successively.
- Embryonated eggs. Information on their origin, identification, quality certificates should be provided.
- General description of the raw materials. Considering the raw materials used in the preparation process from which the drug substance is not directly derived, such as culture media, bovine fetal serum, etc. Submit information on manufacturer(s), quality certificates, controls performed. In the case of raw materials of animal origin, describe the origin and criteria for selection, shipping, and conservation, and submit a certificate on reduction of the risk of transmission of agents related to animal spongiform encephalopathy.

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

Identification of critical steps in-process and controls should be indicated. Selection and justification of critical steps, starting from inoculation up to the production of the drug substance, defining the operational parameters to control during the critical stages, including quality specifications should be included.

Intermediates: Summary of the quality, control, and storage conditions of intermediates isolated during the process should be provided. Stability data supporting storage conditions of intermediates should be provided.

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

A summary of the process validation and evaluation studies should be provided. The actual validation reports may be requested during the review process. If requested, the reports should be filed in this section.

Information should be sufficient to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate the selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification). The information provided should support the current manufacturing process proposed for commercial use, and include data to demonstrate consistency in yield and production, and degree of purity. If an adjuvant is added to the drug substance, validation data should be submitted to demonstrate consistency of manufacturing of the drug substance (e.g. dispersion, pre-determined particle size). Furthermore, for an alum-containing vaccine, study data to demonstrate consistency of adsorption of the drug substance to the adjuvant should be submitted.

The protocol for conducting the study should be described and the results, analysis and conclusions from the executed study (ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced or provided as part of justifying the selection of critical process controls and acceptance criteria.

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. In relation to the change, relevant information on drug substance batches manufactured during development, such as the batch number (and subsequent drug product batch numbers), manufacturing date, scale, and use (e.g. stability, nonclinical, reference material), should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality (e.g. biological activity, impurity profile) of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative

analytical testing on relevant drug substance batches should be provided to determine the impact on the quality of the drug substance (see ICH Q6B for additional guidance). A discussion of the data, a justification for selection of the tests and assessment of the results should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. A cross-reference to the location of these studies in other sections of Module 3 (e.g. Stability, Control of Drug Substance or Drug Product) and/or in other modules of the submission should be included.

A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency should also be provided.

3.2.S.3 Characterisation (name, manufacturer)

Data to determine the structure and physicochemical, immunological, and biological characteristics of the drug substance should be provided.

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

For the intended product and product-related substances, details should be provided, if applicable, on primary sequence, secondary and higher-order structure, post-translational forms (e.g. glycoforms), biological activity, purity, and immunochemical/immunogenicity properties. In addition, depending on the type of vaccine, this may include active or passive immunization studies and challenge studies as appropriate.

A summarized description of the intended product and product related substances and a summary of general properties, characteristic features and characterization data, such as primary and higher order structure and biological activity, should also be provided.

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided. All potential impurities, including process related impurities and degradation products for purified vaccines such as polysaccharide/protein or synthetic peptide vaccines, arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches.

The actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported, for example, using a summary table.

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification. A rationale for excluding any impurity test(s) from routine release testing due to trace levels should also be provided, where applicable.

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification(s) for the drug substance should be provided. For example, the specifications could be presented using a table with the specification reference number, specification approval date, test parameter(s), method type, method code, source, and acceptance limit(s) at release, at the end of shelf-life or for both.

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Information on the analytical procedures used for testing the drug substance should be provided.

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

3.2.S.4.4 Batch Analysis (name, manufacturer)

Description of batches (at least three commercial batches) and results of batch analyses should be provided. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use.

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specification(s) should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Detailed description of the reference standards or materials used and their quality control testing results should be provided. Certificates of analysis should be provided, if applicable.

3.2.S.6 Container Closure System (name, manufacturer)

Full description of the container closure system in which the drug substance will be stored until used for preparing the finished product. The information should include identification of all the materials that constitute the packaging container closure system and their specifications.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including adsorption to container and leaching, and/or safety.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

Should include the study conditions, including all of the storage conditions (temperature, humidity, light) in which the drug substance is evaluated, analytical methods, specifications, summary of results, and conclusions.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

It refers to the continuation of the stability study, including the number of lots to be included in the study each year and the tests to be performed.

3.2.S.7.3 Stability Data (name, manufacturer)

Should include available data from each batch evaluated during stability studies.

3.2.P Drug Product (Name, Dosage Form)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

This should include a description of the drug product, its composition, listing each of the components, drug substance(s), adjuvant, preservatives, stabilizers, and other excipients, stating the function of each of them. For lyophilized products, also include a brief description of the diluents and the container closure system employed for the diluents.

3.2.P.2 Pharmaceutical Development (name, dosage form)

Information on the studies performed to establish the dosage form, formulation, manufacturing process, and the container closure system used for the final product. If an adjuvant is added to the drug product, information and data from the adsorption and desorption study should be submitted,

if applicable. The studies described in this section are different from the routine quality control tests performed in accordance with the product specifications. The following aspects should be included:

3.2.P.2.1 Components of the Drug Product (name, dosage form)

Compatibility of the drug substance with the rest of the components in the drug product should be discussed, including adjuvant, preservative, and stabilizers, as applicable.

3.2.P.2.2 Drug Product (name, dosage form)

Development of the formulation considering the proposed route of administration should be discussed. Physicochemical and biological properties of the product, indicating the relevant parameters for developing the drug product should be included. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical trial batches and primary stability batches should be clearly described and the rationale for the changes provided.

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

Description of the selection and optimization of the manufacturing process, particularly for critical aspects should be provided. Significant differences between the manufacturing process used to produce batches for pivotal clinical trials or primary stability studies and the proposed commercial manufacturing process should be discussed.

3.2.P.2.4 Container Closure System (name, dosage form)

Full description of the container closure system should be provided. The information should include identification of all the materials that constitute the container closure system and their specifications.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug product, including adsorption to container and leaching, and/or safety.

3.2.P.2.5 Microbiological Attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2.P.2.6 Compatibility (name, dosage form)

The compatibility of the drug product with reconstitution diluents (e.g. precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life at the recommended storage temperature and at the likely extremes of concentration.

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

Name, address, and responsibilities of each manufacturer involved, including contract manufacturers for production and quality control with their specific unit block should be provided.

3.2.P.3.2 Batch Formula (name, dosage form)

Provide the formula of the production lot, including a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per lot basis, including overages, and a reference to their quality standards.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

Description of manufacturing process and process controls that must be provided should include:

- Flow chart of manufacturing process. flowchart showing all of the steps in the process and indicating the points at which the material enters the process, identifying the critical steps and control points in the process, intermediate products, and final product.
- Batch and Scale Definition. An explanation of the batch numbering system and scale at each stage of manufacture (e.g. filing, lyophilisation, and packaging).
- Formulation process. Description of the formulation process, the in-process controls, acceptance criteria and the critical steps identified. Information regarding any pooling of bulks or intermediates should be provided.

- Filling process. Description of the filling process, the process controls, acceptance criteria, and the critical steps identified.
- Reprocessing. Description of the procedures established for reprocessing the drug product or any intermediate product; criteria and justification.
- Storage and shipping conditions. When applicable, identify the type and working capacity of the equipment used, areas and buildings (if pertinent), and describe the shipping and storage conditions for the drug product. Additional information should be provided in 3.2.A.1.

3.2.P.3.4 Control of Critical Steps and Intermediates (name, dosage form)

Identified critical steps in the process and controls should be described. The selection and justification of critical steps in the drug product manufacturing process should be included. Tests and acceptance criteria developed to identify the critical steps in the manufacturing process and how they were controlled should be described.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps used in the manufacturing process (e.g., aseptic processing or filling).

The information provided should support the current manufacturing process proposed for commercial use, including in-process test results and data from relevant manufacturing batches to demonstrate consistency in yield and production, and degree of purity.

A summary of the validation study for the extent of reuse and integrity of membranes should be provided, including data to demonstrate consistency in the quality and safety of the drug product.

The suitability of any proposed reprocessing procedures and the criteria for the reprocessing of any intermediate or the drug product should be discussed.

It is also necessary to provide information on the viral safety of the product, when applicable (e.g. products derived from cell lines of human or animal origin).

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

Provide information on the specifications for all of the substances employed in the formulation of the drug product that are different from the drug substance.

3.2.P.4.2 Analytical Procedures (name, dosage form)

Description or literature of reference of the methods used to control excipients should be provided.

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

Copies of analytical validation information are generally not required for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

3.2.P.4.4 Justification of Specifications (name, dosage form)

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

Provide information on the source, origin, description of the quality tests performed, specifications, determination of adventitious agents, and viral safety data.

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). For more detail, see Section 3.2.A.2.

For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the drug products are without risk of transmitting agents of animal spongiform encephalopathies. Materials of animal origin should be avoided whenever possible.

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1. [Reference: ICH Guidelines Q5A, Q5D, Q6B; WHO Technical Report Series, No. 908, Annex 1]

3.2.P.4.6 Novel Excipients (name, dosage form)

For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a vaccine for human use or for a new route of administration, all information on the manufacture, characterization, and control should be submitted under 3.2.A.3 according to the drug

substance and/or drug product CTD format, with a cross-reference to 3.2.A.3 under this section. Cross- references to nonclinical studies (Module 4) and clinical studies (Module 5) supporting the safetyof a novel excipient should also be provided under this section.

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

A copy of the drug product specification(s) from the applicant (as well as the company responsible for the batch release of the drug product, if different from the applicant), dated and signed by authorized personnel (i.e., the person in charge of the quality control or quality assurance department) should be provided in the PD. The specifications should include the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

Two separate sets of specifications may be set out: after packaging of the drug product (release) and shelf life monitoring. Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified.

3.2.P.5.2 Analytical Procedures (name, dosage form)

Information on the analytical procedures used for quality control of the drug product should be provided. Non-pharmacopeia methods, summaries or references may be accepted (e.g. when pharmacopeia methods are unavailable or inappropriate and appropriately validated in-house methods are used). Additional information could be requested.

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

Information on the validation of the analytical procedures for the drug product, including experimental data should be provided in the dossier.

3.2.P.5.4 Batch Analyses (name, dosage form)

Description of batches (at least three lots) and results of batch analyses should be provided. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use.

3.2.P.5.5 Characterization of Impurities (name, dosage form)

Depending on the method used to manufacture the vaccine, a discussion should be provided of all impurities that are potential degradation products and drug product process-related impurities.

3.2.P.5.6 Justification of Specification(s) (name, dosage form)

Provide justification of the specifications proposed for the drug product.

3.2.P.6 Reference Standards or Materials (name, dosage form)

Provide information on the reference standards and/or materials used in the tests to control the drug product.

3.2.P.7 Container Closure System (name, dosage form)

Describe in detail the type and form of container closure systems of the drug product, including the materials of which they are made and quality specifications.

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

Submit the stability study information including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (such as temperature and relative humidity), summary of results for at least three lots of drug product prepared from different lots of drug substance, conclusions, and proposed shelf-life.

It is important to provide additional studies on the stability of the vaccine in intermediate stages in the manufacturing process that require different temperatures from the storage temperature, studies of challenge temperatures, photosensitivity or other specifications, depending on the type of vaccine, evaluated for at least three lots.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

Include the stability program or stability commitment to be carried out once the vaccine is on the market, including the number of lots to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the vaccine evaluated.

3.2.P.8.3 Stability Data (name, dosage form)

Include the complete results of each lot evaluated during stability studies. If applicable, forced degradation studies should be filed within this section.

3.2. A Appendices

3.2.A.1 Facilities and Equipment (name, manufacturer)

A diagram illustrating the production flow, including materials, personnel, waste, and intermediate products in relation to the manufacturing areas; information on adjacent areas related to protection and maintenance of the integrity of the vaccine should be provided. Also, submit information on all of the products prepared and/or handled in the same areas as the product submitted for registration. Describe the procedures to avoid cross-contamination of areas and equipment.

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

Additional, detailed information on evaluation of the safety of the product in relation to adventitious agents of both viral and non-viral origin should be submitted.

3.2.A.3 Excipients

This appendix is required where applicable.

Novel Excipients - For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a vaccine for human use or for a new route of administration, information to support the quality, safety, and suitability for use should be provided in this appendix. This section should be submitted according to the drug substance and/or drug product CTD format described in this document along with cross-references to nonclinical studies (Module 4) and clinical studies (Module 5) supporting the safety of a novel excipient.

Other Excipients - Any extensive drug substance and/or drug product information which is necessary to support the quality, safety, suitability for use, and „approvability" of any (non-novel) non-compendial excipient, and/or any excipient of human or animal origin, should also be provided in this section.

3.2.R Regional Information

Any additional drug substance and/or drug product information specific to a region should be provided in this section of the application.

3.2.R.1 Production Documentation

3.2.R.1.1 Executed Batch Records (name, dosage form, manufacturer)

Summary of executed batch records for three consecutively manufactured or consistency drug product lots from each production site or facility should be provided. Additional lot manufacturing records could be made available upon request.

3.2.R.2 Medical Devices (name, dosage form)

For a vaccine supplied with a medical device, a description of the device(s), including its application and manufacturer should be provided.

3.2.R.3 Lot Release Documentation (name, dosage form)

The proposed test protocol format for the release package, including Certificate of Analysis for the drug substance or drug product, and safety certification for any biological excipient used, if applicable (e.g. a Plasma Certificate), should be provided. The documentation should include the name and title of the delegate with signing authority for lot release.

3.2.R.4 Yearly Biologic Product Report

Summary of yearly Biological Production Report (YBPR) should be provided.

3.3 Literature References

7. MODULE 4: NONCLINICAL STUDY REPORTS

Nonclinical studies should comply with the WHO‟s Guidelines on Nonclinical Evaluation of Vaccines, WHO Technical Report Series No. 927, 2005, or the most recent version. In addition, vaccines containing adjuvants should comply with the WHO Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines.

Additional information for the preparation of this section can be found in ICH M4S (R2).

4.1 Table of Contents of Module 4

The table of contents should be provided.

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

A pharmacodynamics study for a vaccine product is generally conducted to evaluate the immunogenicity of the vaccine or, when animal models are available, the capacity of a vaccine to confer protection. In addition, a pharmacodynamics study may also extend to include the pharmacology of an adjuvant vaccine to provide evidence for the need for the adjuvant.

4.2.1.2 Secondary Pharmacodynamics

Generally not performed for vaccines

4.2.1.3 Safety Pharmacology

The purpose of a safety pharmacology study is to investigate the effects of the candidate vaccine on vital functions. Although not usually required for vaccines, safety pharmacology studies may be recommended in some cases. For example, if data from nonclinical and/or human clinical studies suggest that the adjuvanted vaccine may affect physiological functions (e.g. central nervous, respiratory, and cardiovascular systems, renal functions and body temperature) other than the immune system, safety pharmacology studies should be incorporated into the safety assessment program.

4.2.1.4 Pharmacodynamic Drug Interactions

Generally not performed for vaccines

4.2.2 Pharmacokinetics

Generally not performed for vaccines; however, biodistribution studies may be applicable to the evaluation of vaccine formulations containing new adjuvants or live recombinant viral/bacterial vectors. The feasibility of such studies should be evaluated on a case-by-case basis.

Where pharmacokinetic studies have been performed, the study reports should be provided in the relevant sections below:

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity

Single dose toxicity studies on the final formulated vaccine product, which are applicable to small molecule chemical drugs, are usually not needed for vaccines. Acute effects of administering the vaccine can also be monitored in repeated dose toxicity studies if they are adequately designed (e.g. evaluation is conducted after administration of the first dose).

Alternatively, acute effects can be assessed in a single dose design as part of a local tolerance study.

4.2.3.2 Repeat-Dose Toxicity

Information should be included to justify the study design (e.g. number of animals per group), animal model used (e.g. animal species, age, dose, route of administration) and the parameters monitored.

4.2.3.3 Genotoxicity

Generally genotoxicity studies are not performed for vaccines. However, it may be required if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity. Where genotoxicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including toxicokinetics)

Generally carcinogenicity studies are not performed for vaccines. However, it may be required if there is a component of the vaccine formulation such as a new adjuvant with a new chemical entity. Where carcinogenicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.3.4.1 Long-term studies (not included in repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (not included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity

Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, if the target population for the vaccine includes pregnant women and women of childbearing potential, developmental toxicity studies should be considered unless a scientific and clinically sound argument is put forward by the manufacturer to show that conducting such studies is unnecessary.

Where reproductive and developmental toxicity studies have been performed, the reports should be provided in the relevant sections below:

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

4.2.3.6 Local Tolerance

The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study.

4.2.3.7 Other Toxicity Studies (if available)

Where other toxicity studies have been performed the reports should be provided in the relevant sections below:

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other studies

4.3 Literature References

8. MODULE 5: CLINICAL STUDY REPORTS

Applicant should refer to the most up to date version of the WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations. The WHO recommendations applicable to the specific vaccine should also be considered. Additional information for the preparation of this section can be found in ICH M4E.

Clinical trials in humans are generally classified into three Phases: Phase I, Phase II and Phase III. All studies of human subjects require proper ethical review, in accordance with the Declaration of Helsinki.

Phase I studies are primarily concerned with safety. The Phase I clinical studies carry out initial testing of a vaccine in small numbers (e.g. 20) of healthy adults to test the safety of a vaccine, its tolerability, and, if appropriate, clinical laboratory and immunological parameters.

Phase II studies involve larger numbers of subjects and are intended to provide preliminary information about a vaccine‟s ability to produce its desired effect (usually a specific immune response) in the target population and its general safety.

To fully assess the protective efficacy and safety of a vaccine, extensive Phase III trials are required. Phase III clinical trials are the pivotal studies on which the decision on whether to grant the license is based and sufficient data has to be obtained to demonstrate that a new product is safe and effective for the purpose intended.

Ideally, by the beginning of the Phase III stage of development, a vaccine should have been fully characterized and the final manufacturing process, specifications and batch release testing procedures should have been established. Additional information may be required to support quality changes made post-Phase III studies.

An application for registration may be submitted to the Authority on the basis of the data from Phase III testing and, if approved, the vaccine then becomes commercially available in the country.

The structure of the clinical development programme must be tailored to the type of vaccine and the antigenic content. For example, the clinical evaluation of a vaccine that contains only novel antigen(s) may of necessity be very different from that of a vaccine that contains one or more previously evaluated antigens. Such factors also influence whether clinical protection trials will be required, whether or not they are feasible, or whether an approval may reasonably be based on

immunogenicity data only. In all instances, it is the obligation of the applicant to justify the content and structure of the clinical development programme.

5.1 Table of Contents of Module 5

The table of contents should be provided.

5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided (e.g. type of study, study identifier, location of study report in the application, study objectives, study design and type of control, dosage regimen, route of administration, number and type of subjects, study status). The sequence in which the studies are listed should follow the sequence described in section 5.3 below.

5.3 Clinical Study Reports

Clinical study reports should be provided in the relevant sections below. Additional information on the structure and content of the Clinical Study Report can be found in the ICH E3 Guideline.

5.3.1 Reports of Biopharmaceutical Studies

Biopharmaceutical studies are not generally performed for vaccines. When immunogenicity studies are conducted, reports of bio analytical assays results should be provided in section 5.3.5.

5.3.1.1 Bioavailability Study Reports

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

5.3.1.3 In vitro - In vivo Correlation Study Reports

5.3.1.4 Reports of Bio analytical and Analytical Methods for Human Studies

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials: Not generally performed for vaccines.

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies: Not generally performed for vaccines.

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic Studies

For vaccines, the immunogenicity studies are usually conducted to support the selection of dose, dosage schedule, and formulation of the final product, and the study reports should be provided in Section 5.3.5.

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

Reports of all clinical studies designed to assess the efficacy and safety of the vaccine conducted by the sponsor (or otherwise available), including all completed and all ongoing studies of the vaccine in proposed and non-proposed indications, should be provided in the relevant sections below. This should include the reports of the immunogenicity studies conducted to support the selection of dose, dosage schedule, and formulation of the final product.

For live attenuated vaccines (viral or bacterial, including vaccine vectors), there is a risk of clinically significant infections in the recipient or in contacts. Clinical study reports providing information on shedding, reversion characteristics, and transmission to contacts should be provided in this section.

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Controlled clinical study reports should be sequenced by type of control in the following order:

- Placebo control (could include other control groups, such as an active comparator or other doses)

- No-treatment control (not generally performed for vaccines)
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies, e.g. reports of open label safety studies.

5.3.5.3 Reports of Analyses of Data from More than One Study

Reports of formal integrated analyses, meta-analyses and bridging analyses should be described.

5.3.5.4 Other Study Reports

This section can include the following:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Reports of ongoing studies
- Development Safety Update Reports

5.3.6 Reports of Post-Marketing Experience

Relevant post-marketing studies or information (including all significant safety observations) should be included here.

5.3.7 Case Report Forms and Individual Patient Listings (when submitted)

Case report forms and individual patient data listings that are described in appendices 16.3 and 16.4 in the ICH E3 guideline should be placed in this section, when submitted. They should be presented in the same order as the clinical study reports and indexed by study.

5.4 Literature References

This section should include copies of all references cited in the Clinical Overview and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

ANNEXES

ANNEX I: APPLICATION FORM FOR REGISTRATION (Form-MEMA-001.001)

Food and Drug Authority of Ethiopia P.O.Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

New Application	
Renewal	
Variation to existing marketing authorization (If selected, complete the information below.)	
• Previous registration number	
• Previous registration condition	
• Brief description of change intended	
• Reasons for variations	

B. Details on the product

Proprietary name (trade name)	
Approved generic name (s) (use INN if any)	
Standard claimed (BP, Ph.In, Ph. Eur., USP, IH, etc.)	
Strength(s) per dosage unit	
Dosage form	
Route of administration	
Shelf life (months)	
Storage condition	

Visual description			
Description of container closure			
Packaging and pack size			
Therapeutic category			
Use category	Scheduled Narcotic□		
	Prescription only□		
	Hospital use only□		
	Pharmacy □		
	Over-the-counter (OTC)□		
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per 5ml, etc.)** ** Add/delete as many rows and columns as needed.	Composition	Strength	Function
Complete qualitative and quantitative composition (indicate per batch in Kg, L, etc.)	Composition	Strength	Function

Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes			
Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)			

C. Details on the applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	<<Insert the required information as indicated above>>>

D. Details on active pharmaceutical(s) ingredient(s)

Name of manufacturer	
Street and postal address	
Telephone	
Fax number	
E-mail	
Name of the active ingredient	
Retest period/Shelf life	

E. Details on local agent (representative) in Ethiopia

Name of local agent	
Sub-city and postal address	
Telephone	
Fax number	
E-mail	
Contact person in company Address of company	

F. Details on dossiers submitted with the application

Section of dossier	**Annex, page number, etc.**
Module 1	
Module 2	
Module 3	
Module 4	
Module 5	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANTCOMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

… is correct and true, and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO Guideline, "Good manufacturing practices for biological products," is applied in full in all premises involved in the manufacture of this product.
2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.
3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.
4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications before it is released for manufacturing purposes.
5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.
6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for manufacturing purposes.
8. Each batch of the finished product is either tested or certified against the full specifications in the accompanying documentation and complies fully with the release specifications *before it is released for sale.*
9. The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training."
10. The procedures for control of the finished product have been validated for this formulation.
11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.
12. The market authorization holder has a standard operating procedure for handling batch recalls of its products.
13. All the documentation referred to in this Certificate is available for review during a GMP inspection.
14. Any clinical trials were conducted according to WHO"s "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products."

Signature_____

Name _____

Position in company (print or type) _____

Date: _____

ANNEX II: CERTIFICATE OF PHARMACEUTICAL PRODUCTS[1]

This certificate conforms to the format recommended by the World Health Organization

(General instructions and explanatory notes attached)

Certificate No. _____

Exporting (certifying country): _____

Importing (requesting country): _____

1. Name and dosage form of the product: _____

1.1. Active ingredient(s)[2] and amount(s) per unit dose[3]: _____

For complete composition including excipients, see attached[4]: _____

1.2. Is this product licensed to be placed on the market for use in the exporting country?[5]

yes/no (*Key in as appropriate*)

1.3 Is this product actually on the market in the exporting country? (*Key in as appropriate*)

yes/no/unknown

If the answer to 1.2. is **yes**, continue with section 2A and omit section 2B. If the answer to 1.2 is no, omit section 2A and continue with section 2B[6]:

2.A.1. Number of product license[7] and date of issue:

_____

2.A.2. Product license holder (name and address):

_____

2.A.3. Status of product license holder:[8]

a/b/c *(Key in appropriate category as defined in note 8)*

2.A.3.1. For categories (b) and (c), provide the name and address of the manufacturer producing thedosage form[9]: _____

2.A.4. Is a summary basis for approval appended?[10]

yes/no (*Key in as appropriate*)

2.A.5. Is the attached, officially approved product information complete and consonant with the license?[11]

yes/no/not provided (*Key in as appropriate*)

2.A.6. Applicant for Certificate, if different from license holder (name and address):[12] _____

2.B.1. Applicant for Certificate (name and address): _____

2.B.2. Status of applicant:

a b/c (*Key in appropriate category as defined in footnote 8)*

2.B.2.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form[9]:

2.B.3. Why is marketing authorization lacking?

not required/not requested/under consideration/refused (*Key in as appropriate*)

2.B.4. Remarks:[13]

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which thedosage form is produced?

If not or not applicable, proceed to question 4.

yes/no/not applicable[14] (*Key in as appropriate*)

3.1. Periodicity of routine inspections (years): _____

3.2. Has the manufacture of this type of dosage form been inspected?

yes/no

3.3. Do the facilities and operations conform to good manufacturing practices (GMP) as recommendedby the World Health Organization (WHO)?[15]

yes/no/not applicable[14] (*Key in as appropriate*)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product:[16]

yes/no *(Key in as appropriate)*

If no, explain: _____

Address of certifying authority: _____

Telephone: _____

Fax no.:_____

E-mail: _____

Name of authorized person: _____

Signature: _____

Stamp and date: _____

General instructions

Please refer to the Guideline for full instructions on how to complete this form and for information onthe implementation of the Scheme.

This form should always be submitted as a hard copy, with responses printed in type rather thanhandwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

1 This Certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the Certificate in the exporting country. It is for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2 Use, whenever possible, the International Nonproprietary Names (INNs) or national nonproprietary names

3 The formula (complete composition) of the dosage form should be given on the Certificate or should be appended.

4 Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-license holder.

5 When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is specified in the product license.

6 Sections 2A and 2B are mutually exclusive.

7 Indicate, when applicable, if the license is provisional, or the product has not yet been approved.

8 Specify whether the person responsible for placing the product on the market:

(a) manufactures the dosage form;

(b) packages and/or labels a dosage form manufactured by an independent company; or,

(c) is not involved in any of the above.

9 This information can only be provided with the consent of the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product license.

If the production site is changed, the license has to be updated or it is no longer valid.

10 This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

11 This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC).

12 In this circumstance, permission for issuing the Certificate is required from the product-license holder. This permission has to be provided to the Authority by the applicant.

13 Please indicate the reason that the applicant has provided for not requesting registration.

(a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases —not endemic in the country of export;

(b) the product has been reformulated with a view to improving its stability under tropical conditions;

(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products inthe country of import;

(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient; or,

(e) any other reason (please specify).

14 Not applicable means the manufacture is taking place in a country other than that issuing the product Certificate and inspection is conducted under the aegis of the country of manufacture.

15 The requirements for good practices in the manufacture and quality control of drugs referred to in the Certificate are those included in the Thirty-second Report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

16 This section is to be completed when the product-license holder or applicant conforms to status (b) or (c), as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances, the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

ANNEX III: SUMMARY OF PRODUCT CHARACTERISTICS

(With proposed sentence patterns and illustrative examples)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

   {(Invented) name of product <strength><pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

   For excipients, see 6.1.

3. PHARMACEUTICAL FORM

4. CLINICAL PARTICULARS

   4.1. Therapeutic indications

   <This pharmaceutical product is for diagnostic use only. >

   4.2. Posology and method of administration [*See example below.*]

   Adults

   Children and adolescents (4 to 17 years of age)

   General administration recommendations

   Special dosing considerations in adults

   4.3. Contraindications

   <Hypersensitivity to the API(s) or to any of the excipients <or {residues}>

   4.4. Special warnings and special precautions for use [*See example below.*]

   Drug interactions

   Acute hemolytic

   Hyperglycemia

   Patients with coexisting conditions

   4.5. Interaction with other FPPs and other forms of interaction [*See example below.*]

   Rifabutin)

   Ketoconazole)

   Itraconazole)

   Nevirapine)

   HMG -CoA reductase inhibitors)

   Rifampicin)

4.6. Pregnancy and lactation [*See example below.*]

Use during pregnancy)

Use during lactation)

4.7. Effects on ability to drive and use machines

< {Invented name} has <no or negligible influence><minor or moderate influence><major influence> on the ability to drive and use machines.> [describe effects where applicable]

<No studies on the effects on the ability to drive and use machines have been performed.><Not relevant.>

4.8. Undesirable effects [*See example below.*]

Laboratory test findings)

Post-marketing experience)

4.9. Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: {group}

ATC code: {code}

Mechanism of action

Microbiology (when applicable)

Drug resistance (when applicable)

Cross resistance (when applicable)

Pharmacodynamic effects

Adults

Pediatric patients

5.2. Pharmacokinetic properties

Absorption

Distribution

Biotransformation

Elimination

Characteristics in patients

5.3. Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.><Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.>

Mutagenicity

Carcinogenicity

Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients [*See example below.*]

Capsule content)

Capsule shell)

Printing ink)

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>

<This pharmaceutical product must not be mixed with other pharmaceutical products except those mentioned in 6.6.>

6.3. Shelf life

<...><6 months><...><1 year><18 months><2 years><30 months><3 years><...>

6.4. Special precautions for storage

<Do not store above <25°C> 30°C»

<Store at 2°C - 8°C (in a refrigerator» <Store in a freezer>

<Do not <refrigerate><or><freeze»

<Store in the original <package><container» <Keep the container tightly closed>

<Keep the container in the outer carton>

<No special precautions for storage>

<in order to protect from <light><moisture»

6.5. Nature and contents of container

<Not all pack sizes may be marketed.>

6.6. Instructions for use and handling <and disposal>

<No special requirements.>

7. MARKETING AUTHORISATION HOLDER
8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS
9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION OF EXPORTING COUNTRY
10. DATE OF REVISION OF THE TEXT

ANNEX IV: REQUIREMENTS FOR REGISTRATION OF PRODUCTS ACCEPTED BY A STRINGENT REGULATORY AUTHORITY

General Principle

Stringent Regulatory Authorities are national medicine regulatory authorities and international organization recognized and listed as a stringent by the EFMHACA. When the product application has been submitted and accepted in countries such as United States of America, Canada, Australia, Norway, Finland, France Denmark, Netherlands, Austria, Japan, EMA, Switzerland, Belgium, Germany, Italy, Ireland, UK, and WHO Prequalification Programme are considered to be products registered with a Stringent Regulatory Authority (SRA).

The purpose of this guidance is neither to eliminate the requirement of dossier submission nor to limit the Authority for full assessment of the product, whenever deemed to be necessary, the main purpose is to introduce a procedure that will facilitate the registration of innovator products as well as products accepted through the WHO Prequalification Programme (PQP) in order to enhance the availability of the vaccine to the public.

The rationale behind the introduction of these procedures is that:

1. Most of the requirements and principles stipulated in this Guideline are derived from the guidance developed by ICH regions and associated countries, and from WHO Guidelines;
2. Whenever necessary, full assessment of the dossiers of the innovators can be done at any time; and,
3. The clinical studies, as well as the acceptance of the medicines for the general public health benefit, have been accepted.

An applicant claiming to have a registration certificate issued by an SRA, as defined above, should submit complete dossiers. At the time of registration by the Authority, the information that needs to be assessed is:

1. Full information under Administrative and product information section of this Guideline
2. Public assessment report(s) and/or final acceptance letter issued by a national regulatory authority in an ICH region and associated countries (e.g., summary of product characteristics and Certificate of Pharmaceutical Product);

3. In the case of a WHO Prequalified product, the final acceptance letter and a copy of the WHO Public Assessment Report (WHOPAR);
4. A Quality Assurance-certified copy of the Marketing Authorization issued by the relevant SRA;
5. If the composition/formulation, strength, specifications, etc., are different from the prequalified product or the product for which the marketing authorization Certificate was issued recognized SRA, arguments and/or data to support the applicability of the Certificate(s), and demonstration of clinical equivalence;
6. If the primary packaging material of the product is different from that approved by the national regulatory authorities of the ICH regions and associated countries or WHO PQP, then all stability testing data;
7. Written commitment letter to notify the Authority that whenever a pending variation, notice of concern, withdrawal, or recall is initiated, the same shall be communicated to the Authority; and,
8. Evidence of a minimum of five (5) years of current and continuous manufacturing experience and a copy of the last Annual Product Report. Specific issues on manufacturing experience will be address on case-by-case basis by the Authority.

Reference

This guideline is adapted from Guidance Document Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application, Health Canada, 2016